Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave. Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review

Date	Refer to signature date at the end.
From	Silvana Borges, MD, Clinical Team Leader and Deputy Division Director Rigoberto Roca, MD, Division Director
NDA	208969
Applicant	Amphastar Pharmaceuticals, Inc.
Date of Original Submission	April 19, 2016 Complete Response letter issued February 17. 2017
Date of Complete Response Submission	September 7, 2022
PDUFA Goal Date	March 7, 2023
Proprietary Name	To be determined
Established or Proper Name	Naloxone Hydrochloride
Dosage Form	Nasal Spray; 4 mg of naloxone hydrochloride in 0.25 mL
Applicant Proposed Indication/Populations	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
Applicant Proposed Dosing Regimen	• Seek emergency medical care immediately after use. • Administer a single spray of Naloxone Hydrochloride Nasal Spray to adults or pediatric patients intranasally into one nostril. • Administer additional doses of Naloxone Hydrochloride Nasal Spray using a new nasal spray device with each dose if the patient does not respond or responds and then relapses into respiratory depression. Additional doses of Naloxone Hydrochloride Nasal Spray may be given every 2 to 3 minutes until emergency medical assistance arrives. • Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.
Regulatory Action	Approval

Review Team

Discipline	Primary/Secondary/Tertiary Assessment
Office of Pharmaceutical Quality	
Chemistry, Manufacturing, and Control (CMC)	Zhixing Shan/ Gaetan Ladouceur Mari Chelliah/ Valerie Amspacher Qiang Han/ Kamal Tiwari
Microbiology	George Arhin/ Elizabeth Bearr
Pharmacology/Toxicology	Carlic Huynh/Nikunj Patel/Newton Woo/Dan Mellon
Clinical Pharmacology	Srikanth Nallani/ Yun Xu
Clinical	Corinne Ahmar/Silvana Borges
ADL	Lisa Basham
PM	Namrata Thakkar/Matthew Sullivan
Consults	
DMEPA	Damon Birkemeier/ Oluwamurewa Oguntimein (Murewa)/Valerie Vaughn
OSE PM	Carol Corbie
OPDP	LaToya Shenee Toombs
DPV	Sarah Kang/ Mallika Mundkur
DPMH	Ndidi Nwokorie/Mona Khurana
CDRH	Kyran Gibson
Patient Labeling	Ruth Mayrosh/Barbara Fuller

1. Benefit-Risk Assessment

Opioid overdose is a major public health problem in the United States leading to tens of thousands of deaths every year. Naloxone is a nonselective opioid receptor antagonist with high affinity for the mu-opioid receptor developed to reverse life-threatening opioid overdose and prevent hypoxia associated with injury and death.

There are many FDA approved naloxone products for use in adults and pediatric patients in the community, of which the following are currently available in the market: Narcan (naloxone nasal spray 4 mg, NDA 208411) approved in 2015; Kloxxado **(**naloxone nasal spray 8 mg, NDA 212045) and Zimhi (naloxone 5 mg, pre-filled syringe for intramuscular or subcutaneous injection, NDA 212854), both approved in 2021. Several generic naloxone 4 mg nasal spray products are also available for use in the community.

The Applicant (Amphastar Pharmaceuticals, Inc.) resubmitted NDA 208969 on September 7, 2022, pursuing approval of naloxone hydrochloride nasal spray 4 mg in 0.25 ml for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients through the 505(b)(2) pathway. Naloxone nasal spray 4 mg/0.25ml is a drug-device combination intended for use in the community. In this resubmission, the Applicant relies on FDA's previous findings of efficacy and safety for Narcan injection (naloxone hydrochloride 0.4 mg, NDA 16636) and naloxone injection 2 mg (ANDA 072076).

The efficacy of Naloxone NS 4 mg/0.25ml was evaluated in one PK study comparing the systemic exposure to naloxone following the administration of Naloxone NS 4 mg/0.25ml, naloxone 0.4mg IM, naloxone 2mg IV, and naloxone nasal spray 10 mg/0.25 ml. In this PK study, Naloxone NS 4 mg/0.25ml demonstrated higher concentrations and greater partial AUCs at the early absorption phase, greater C_{max}, greater AUC_{0-t} and AUC_{0-inf} than Narcan injection. The naloxone concentrations during the early absorption phase, and the C_{max}, AUC_{0-t} and AUC_{0-inf} values with Naloxone NS 4 mg/0.25ml were all lower than with naloxone 2 mg IV. Therefore, Naloxone NS 4 mg/0.25ml has demonstrated naloxone systemic exposure between that of Narcan injection 0.4 mg IM and naloxone injection 2 mg IV, supporting the Applicant's reliance on efficacy findings of Narcan injection and systemic safety findings of naloxone injection 2 mg IV.

The main risks of naloxone are severe precipitated opioid withdrawal and associated cardiovascular risks. Cardiac arrhythmias, cardiac arrest and death have been reported following the reversal of opioid-induced respiratory depression and have primarily occurred in patients with pre-existing opioid dependence and cardiovascular disorders. Despite these known risks, the Division have previously found the benefit-risk assessment to be favorable for naloxone products for intranasal administration of similar or higher strengths than Naloxone NS 4 mg/0.25ml (e.g., Narcan nasal spray 4 mg and Kloxxado nasal spray 8 mg). The extensive use of these products in the community has also shown that the benefit of reversing a life-threatening opioid overdose outweighs their risks.

The clinical data for Naloxone NS 4 mg/0.25ml has shown a similar safety profile for this product compared to other naloxone products in the adult population.

Regarding the pediatric population, naloxone products intended for use in the community are expected to be used in the entire pediatric age range. The dosing volume of 0.25 ml in Naloxone NS 4 mg/0.25ml is 2.5 times higher than the highest dosing volume in approved naloxone products for intranasal administration (i.e., 0.1 ml). Therefore, there were concerns about the safety and possible impact on efficacy of a dosing volume of 0.25 ml administered intranasally to pediatric patients. To address these concerns, the Applicant submitted 1) a retrospective observational safety study of different medications administered intranasally at dosing volumes >0.25 ml in pediatric patients 3 years of age and younger; and 2) modeling data estimating the nasal spray run-off following the administration of 0.25 ml intranasally in infants. The data from these pediatric studies, along with the efficacy and safety data from the studies in adults, addressed our efficacy and safety concerns related to the use of Naloxone NS 4 mg/0.25ml in the pediatric population of all ages down to birth.

The Applicant has demonstrated the safety and efficacy of Naloxone NS 4 mg/0.25ml for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients. The regulatory action for this application is Approval.

2. Background

The Applicant (Amphastar Pharmaceuticals, Inc.) developed Naloxone NS 4 mg in 0.25ml, referred as "Naloxone NS 4 mg/0.25ml" in this review, for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients. The product is a single-use, drug-device combination product intended to be used in the community by laypersons to rescue patients experiencing the life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention.

The Applicant's original formulation contained (b) (4) mg of naloxone hydrochloride in (b) (4) ml. Of note, the highest dosing volume in an approved naloxone product for intranasal administration is 0.1 ml. In interactions with the Applicant preceding the original NDA submission, the FDA expressed concerns about the safety and possible impact on efficacy of a dosing volume of (b) (4) ml administered intranasally to pediatric patients. The original NDA was submitted on April 19, 2016 and received a Complete Response (CR) on February 17, 2017, due to lack of support for the safety and efficacy of the (b) (4) ml dosing volume in pediatric patients, and deficiencies related to the human factors validation study (b) (4)) and CMC specifications. Following this CR action, two Type A meetings (on May 15 and November 28, 2017) and one Type C meeting (on March 18, 2020) were conducted between the Applicant and the FDA to discuss pathways to resolve the deficiencies of the original NDA. In these meetings, among other exchanges, the Applicant proposed or agreed to:

- Change the naloxone dose in their product from (b) (4) mg to 4 mg.
- Change their naloxone formulation from (b) (4) to 4 mg in 0.25 ml.
- Change the device to a pre-assembled device design, (b) (4)
- Conduct a comparative bioavailability study and a study of the effects on olfactory function with the new formulation (i.e., 4 mg/0.25 ml).
- Provide additional information to support the safety and efficacy of the new formulation in pediatric patients.

The Applicant resubmitted the NDA on September 7, 2022, pursuing approval of Naloxone NS 4 mg/0.25ml, through the 505(b)(2) pathway. The listed drug is Narcan injection (naloxone hydrochloride 0.4 mg, NDA 16636). In support of their 505(b)(2) application, the Applicant submitted bioavailability data comparing Naloxone NS 4 mg/0.25ml with naloxone 0.4mg IM, naloxone 2mg IV, and naloxone nasal spray 10 mg/0.25 ml, to establish a scientific bridge to the efficacy and safety findings of Narcan injection for the proposed indication. The Applicant also submitted safety data from a study evaluating the effects of Naloxone NS 4 mg/0.25ml on olfactory function. To address the concerns related to the use of a dosing volume of 0.25 ml in the pediatric population, the Applicant submitted 1) a retrospective observational safety study of different medications administered intranasally at dosing volumes >0.25 ml in pediatric patients 3 years of age and younger; 2) modeling data estimating the nasal spray run-off following the administration of 0.25 ml intranasally to infants.

3. Product Quality

The CMC team conducted a full review of this resubmission as the Naloxone NS 4 mg/0.25ml product constitutes a new formulation and new device, compared to the product in the original NDA. According to the review by Valerie Amspacher, the CMS team leader, no deficiencies have been identified in the drug substance, drug product, manufacturing, or microbiology of the product. All CMC disciplines recommend approval of Naloxone NS 4 mg/0.25ml. Refer to the review by Valerie Amspacher dated February 16, 2023, for more details.

For Naloxone NS 4 mg/0.25ml, the Applicant redesigned the device developed for the original product, i.e., naloxone nasal spray (b) (4). The original device (b) (4) was deemed inadequate for the intended use. The redesigned device for Naloxone NS 4 mg/0.25ml comes preassembled and ready to be used. The Naloxone NS 4 mg/0.25ml device has been deemed acceptable for the intended use.

4. Nonclinical Pharmacology/Toxicology

According to Dr. Carlic Huynh's review, no pharmacology/toxicology deficiencies were identified in the original submission of this NDA, as noted in the nonclinical review dated January 23, 2017. There were no new nonclinical studies submitted in this NDA. The formulation contains 4 mg of naloxone hydrochloride in 0.25 mL (16 mg/mL) with no novel excipients. The drug substance and drug product specifications, elemental impurities and (b) (4) assessments are acceptable. The extractable/leachables data supports the safety of the container closure system. Therefore, Dr. Huynh concludes that there are no nonclinical concerns with the Naloxone NS 4 mg/0.25ml product and recommends its approval.

Refer to Dr. Carlic Huynh's review dated March 1, 2023, for more details.

5. Clinical Pharmacology

According to the review by Dr. Srikanth Nallani dated February 9, 2023, the Applicant conducted Study API-N002-CL-A3 (Study A3) comparing the systemic exposure to naloxone following the administration of Naloxone NS 4 mg/0.25ml, naloxone 0.4 mg IM, naloxone 2 mg IV, and naloxone 10 mg/0.25 ml IN, in support of this application. Although included in Study A3, the Applicant is not seeking approval of the 10 mg/0.25 ml intranasal naloxone product. Given that Narcan injection is not currently marketed, the Applicant utilized two generic products to evaluate the efficacy and safety of Naloxone NS 4 mg/0.25ml in Study A3: naloxone injection 0.4 mg (Hospira, ANDA 070256) administered IM and naloxone injection 2 mg (Amphastar/IMS, ANDA 072076) administered through IV infusion. The Applicant confirmed that the final to-be-marketed product (formulation and device) for Naloxone NS 4 mg/0.25ml was used in the comparative bioavailability Study A3.

The Applicant's strategy appeared to be one of demonstrating that the plasma naloxone concentrations with Naloxone NS 4 mg/0.25ml fall between the plasma concentrations achieved with the approved doses of naloxone 0.4 mg IM injection and naloxone 2 mg IV injection. In Study A3, the mean $AUC_{0\text{-}2min}$, $AUC_{0\text{-}3min}$, $AUC_{0\text{-}5min}$, and $AUC_{0\text{-}10min}$ for a single

dose of Naloxone NS 4 mg/0.25ml were 117.5%, 159%, 208%, and 292%, respectively, of that for a single dose of 0.4 mg of naloxone IM. The lower limits of the 90% CIs for the partial $AUC_{0\text{-}30min}$ were all greater than 80%, with the exception of $AUC_{0\text{-}2min}$, for which the lower 90% CI was lower than 80%. Dr. Nallani interpreted that this result is likely due to the sample size not being sufficiently large and pointed to the data providing further evidence that Naloxone NS 4 mg/0.25ml leads to higher systemic exposure than the IM comparator during the early absorption phase (e.g., 1, 2, 3, 5, 10 min post-dose). The early partial AUC at 5 minutes was also higher with Naloxone NS 4 mg/0.25ml than with the intramuscular naloxone injection. Taken together, Dr. Nallani concluded that these observations support that Naloxone NS 4 mg/0.25ml is expected to deliver effective levels of naloxone for the proposed indication. The naloxone concentrations during the early absorption phase, and the C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ values with a single dose of Naloxone NS 4 mg/0.25ml were all lower than with a single 2 mg dose of naloxone IV.

The Office of Study Integrity and Surveillance (OSIS) determined that inspections in the clinical site and the analytical site for Study A3 were not needed at this time since inspections recently conducted at these sites fall within the surveillance interval.

Based on all these considerations, Dr. Nallani concluded that the Applicant has established a scientific bridge between Naloxone NS 4 mg/0.25ml and the listed drug (Narcan injection, naloxone hydrochloride 0.4 mg, NDA 16636) and recommended approval of this application.

Refer to Dr. Nallani's review for more details.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The efficacy of Naloxone NS 4 mg/0.25ml is supported by a scientific bridge to the listed drug Narcan injection (naloxone hydrochloride 0.4 mg) through one bioavailability pharmacokinetic study (Study A3) comparing Naloxone NS 4 mg/0.25ml and Narcan injection. Naloxone NS 4 mg/0.25ml demonstrated higher concentrations and greater partial AUCs at the early absorption phase, greater C_{max}, greater $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ than Narcan injection. These findings support the Applicant's reliance on FDA's previous findings of efficacy for Narcan injection in adults.

However, the higher dosing volume of Naloxone NS 4 mg/0.25ml (i.e., 0.25 ml) compared to the highest dosing volume in other approved naloxone nasal spray products (i.e., 0.1 ml), raised concerns about the potential run-off of the Naloxone NS 4 mg/0.25ml dose when administered to pediatric patients, particularly in the 0-3 years age range. The run-off of the Naloxone NS 4 mg/0.25ml dose could potentially decrease the efficacy of the product by the partial loss of the administered dose. The Applicant submitted data to address this concern. Refer to Section 10 of this review for a detailed discussion of such data.

8. Safety

According to Dr. Corinne Ahmar's clinical review, the Applicant provided new clinical safety data from Study A3. In this study, there were no clinically significant adverse events and no new safety signals with Naloxone NS 4 mg/0.25ml were identified.

It is of note that naloxone injection 2 mg (Amphastar/IMS, ANDA 072076) is an approved product whose benefit-risk assessment has been deemed favorable. The Applicant has shown that the systemic exposure for Naloxone NS 4 mg/0.25ml is lower than for naloxone injection 2 mg. These pharmacokinetic data, along with the clinical data from Study A3 supports the systemic safety of Naloxone NS 4 mg/0.25ml.

Regarding local toxicity, the clinical evaluation of the nasal cavity in participants of Study A3 did not raise any safety concerns. The Applicant also conducted Study API-N002-CL-A4 (Study A4) to evaluate the effects of Naloxone NS 4 mg/0.25ml on olfactory function. This was a randomized, double-blinded, crossover study that evaluated the effects on olfactory function of a single dose of Naloxone 10 mg/0.25ml or placebo administered intranasally to 28 healthy volunteers. It is of note that this study utilized a 10 mg/0.25 ml naloxone formulation with a concentration of 40mg/ml, while the to-be-marketed drug product contains 4 mg of naloxone with a lower concentration of 16 mg/ml.

The olfactory function of study subjects was assessed using the University of Pennsylvania Smell Identification Test (UPSIT). Two subjects who had received placebo and one subject who had received Naloxone NS 10 mg/0.25ml had a decrease in their olfactory performance observed from normosmia to mild microsmia (olfactory performance score change from 5 to 4). Dr. Ahmar concluded that no significant change in olfactory function was observed following administration of a single dose of Naloxone NS 10 mg/0.25ml with a concentration of 40 mg/ml. Given that this naloxone dose and concentration exceeds that of Naloxone NS 4 mg/0.25ml, these findings support the local safety of this product.

As mentioned before, the 0.25 ml dosing volume of Naloxone NS 4 mg/0.25ml raised concerns about the potential run-off of the Naloxone NS 4 mg/0.25ml dose when administered to pediatric patients. The run-off of the Naloxone NS 4 mg/0.25ml dose could have adverse consequences (e.g., aspiration), particularly in infants. The Applicant submitted data to address this concern. Refer to Section 10 of this review for a detailed discussion of such data.

9. Advisory Committee Meeting

No advisory committee meeting was held because there were no issues identified that required input from an advisory committee.

10. Pediatrics

The device used for Naloxone NS 4 mg/0.25ml was redesigned following FDA's recommendations as a pre-assembled device and deemed adequate for use in pediatric patients of all ages down to birth.

Naloxone products intended for use in the community (e.g., Narcan NS 4 mg) are approved for use in the entire pediatric age range. The safety and effectiveness of naloxone for the emergency treatment of known or suspected opioid overdose in pediatric patients of all ages has been previously established based on pharmacokinetic evaluations and extrapolation of efficacy and safety data from the adult population.

The efficacy of Naloxone NS 4 mg/0.25ml in the pediatric population is extrapolated from Study A3 in adults which demonstrated that the systemic exposure of Naloxone NS 4 mg/0.25ml is higher than that of Narcan injection (naloxone 0.4 mg IM). However, the dosing volume of 0.25 ml in the proposed product is 2.5 times higher than the highest dosing volume in approved naloxone products for intranasal administration (i.e., 0.1 ml). The Applicant evaluated the extent of run-off when administering a 0.25 ml dose intranasally to pediatric patients using CT scan data of the pediatric nasal airway anatomy from 6 children (5 of them younger than 1 year) and computational simulation using age-dependent nose-throat airway models. These simulations were conducted to estimate the run-off fractions from different nasal spray volumes and predicted that a minimal (~1%) run-off would occur with a spray volume of 0.25 ml, even when this spray volume is administered to neonates. However, the review team identified possible shortcomings in the Applicant's model: 1) the Applicant's predicted run-off fraction for the 0.5 ml volume was ~30% different from the run-off fraction for 0.5 ml found in the literature; 2) the Applicant's model used an airflow of 1.72 L/min (20% of estimated normal rate), which may not reflect the airflow during an opioid overdose, including a possible airflow of near zero in apneic patients.

Following our request, the Applicant incorporated the parameters from the literature into their model and demonstrated that their results were similar to the published data, therefore increasing the credibility of their model. They also estimated the run-off fractions using a range of airflow rates (0%, 10%, 30%, and 40% of estimated normal rate). This sensitivity analysis showed little impact from these airflow rates on the predicted run-off fraction. The highest predicted run-off fraction was 3.9% of the 0.25 ml volume administered intranasally in the 10-day old model. If this run-off is considered as a naloxone dose loss, the actual naloxone dose delivered when administering Naloxone NS 4 mg/0.25ml to a newborn (the worst-case scenario) would be 3.84 mg (i.e., 96.1 % of the dose) which is still higher than the approved 2-mg naloxone NS dose (NDA 208411) previously deemed effective for the intended indication. All these data support the efficacy of Naloxone NS 4 mg/0.25ml in the pediatric population of all ages down to birth.

The systemic safety of Naloxone NS 4 mg/0.25ml in the pediatric population is extrapolated from Study A3 in adults which demonstrated that the systemic exposure of Naloxone NS 4 mg/0.25ml was lower than that single 2 mg dose of naloxone IV. However, there were safety concerns related to the use of a dosing volume of 0.25 ml by the intranasal route in children, particularly in those 3 years of age and younger.

To support the safety of Naloxone NS 4 mg/0.25ml dosing volume, the Applicant conducted Study API-N002-CL-C, a retrospective observational pediatric study using electronic medical records (EMRs) from 4 US hospitals (Study C). This retrospective analysis included EMRs of 562 children aged 0-3 years who received medications through the intranasal (IN) route at volumes ranging from 0.25 ml to 3.90 ml. Of note, 37 out of the 562 patients (6.6%) were ≤1 year of age. The IN-administered medications were midazolam, fentanyl, ketamine, dexmedetomidine and/or additional sedative and analgesics. The study endpoint was adverse drug events (ADE) related to IN dosing, particularly any ADE defined as respiratory compromise (e.g., aspiration). No ADE related to the IN dosing volume were identified. These findings are supportive of the safety of the 0.25 ml IN spray volume in the youngest patients.

All these considerations led to the conclusion that the Applicant has addressed our efficacy and safety concerns related to the use of Naloxone NS 4 mg/0.25ml in the pediatric population of all ages down to birth.

Refer to Dr. Ahmar's clinical review and consult reviews by the Division of Pediatrics and Maternal Health (dated February 7, 2023) and the Division of Applied Regulatory Science (attached to Dr. Ahmar's review) for more details on these pediatric data.

Based on her review of the totality of the safety and efficacy data submitted in this NDA resubmission, Dr. Corinne Ahmar recommended approval of this application. We agree with her recommendation.

11. Other Relevant Regulatory Issues

In the original NDA submission, the Division of Medication Error Prevention and Analysis (DMEPA) had identified deficiencies in the two human factors validation studies submitted in support of the application. Following the 2017 CR, DMEPA provided advice to the Applicant on several aspects of the use of their device, including the review of a new human factors validation study, which was submitted to support the NDA resubmission subject of this review. Upon review of this new human factor validation study report in this review cycle, DMEPA concluded that the study did not demonstrate use errors, use difficulties, or close calls with any tasks, except for Step 7 in the instruction for use (IFU). However, DMEPA determined that the IFU Step 7 language could be improved to avoid misinterpretation and additional human factor data would not be necessary. The Applicant implemented DMEPA's labeling recommendations. DMEPA recommended approval of this application.

Please refer to the review from DMEPA (dated February 9, 2023) for details.

12. Labeling

The proposed prescribing information for Naloxone Hydrochloride Nasal Spray is based on the approved labeling for the listed drug Narcan injection (NDA 016636). The Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP) and the Division of Pediatric and Maternal Health (DPMH) were consulted regarding the proposed labeling. Dr. Ahmar, the clinical reviewer, identified necessary

revisions throughout the label to reflect the adverse events findings with Naloxone NS 4 mg/0.25ml and also to make this product labeling consistent with most recently approved naloxone nasal spray products. CMC, DMEPA, clinical pharmacology, and pharmacology toxicology also requested labeling revisions from the Applicant. The Applicant agreed to our labeling revisions or provided adequate justification for their labeling language and agreement was reached with the Applicant on labeling for Naloxone NS 4 mg/0.25ml.

13. Postmarketing Requirements

No postmarketing study is required for this application at this time. All the information necessary for the safe and effective use of Naloxone NS 4 mg/0.25ml for the intended indication has been provided in this NDA resubmission.

14. Comments to the Applicant

No comments to the Applicant are necessary.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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